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# Relation Between Dose of Loop Diuretics and Outcomes in a Heart Failure Population: Results of the ESCAPE Trial

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## Abstract

**Background—** We examined the relation of maximal in-hospital diuretic dose to weight loss, changes in renal function, and mortality in hospitalised heart failure (HF) patients.

**Methods—** In ESCAPE, 395 patients received diuretics in-hospital. Weight was measured at baseline, discharge, and every other day before discharge. Weight loss was defined as the difference between baseline and last in-hospital weight. Mortality was assessed using a log-logistic model with non-zero background.

**Results—** Median weight loss: 2.8 kg (0.7, 6.1); mean: 3.7 kg (22% of values <0). Weight loss and maximum in-hospital dose were correlated ($p = 0.0007$). Baseline weight, length of stay, and baseline brain natriuretic peptide were significant predictors of weight loss. After adjusting for these, dose was not a significant predictor of weight loss. A strong relation between dose and mortality was seen ($p = 0.003$), especially at >300 mg/day. Dose remained a significant predictor of mortality after adjusting for baseline variables that significantly predicted mortality. Correlation between maximal dose and creatinine level change was not significant ($r = 0.043$; $p = 0.412$)

**Conclusions—** High diuretic doses during HF hospitalisation are associated with increased mortality and poor 6-month outcome.

### Keywords

diuretics; heart failure; outcomes

Loop diuretics are often given early in the course of treatment of hospitalised decompensated heart failure (HF) patients. Because clinical trial data defining the ideal diuretic dose are lacking, dosing is largely based on iterative increases with observation of patients for urine output. Factors that typically drive dose selection include diuretic dose before admission, renal function, severity of volume overload, and whether the patient is

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believed to be diuretic resistant. The relation between weight loss, symptomatic improvement, adverse events, and dose has not been well described in these patients.

Diuretic dose selection may have important implications for long-term outcomes. Worsening renal function is a known predictor of poor outcomes in this population (1,2). Renal insufficiency can be induced or worsened by the administration of diuretics. It is unknown if a relation exists between diuretic-induced worsening renal function and clinical outcomes. In addition, the cardio-renal syndrome is increasingly recognized as an important component of HF pathophysiology (3,4). Several retrospective studies have also suggested that chronic diuretic use was a predictor of worse outcomes, even after adjustments for other markers of severity (5,6). However, the association between high doses of diuretics and outcomes of patients with acute HF has not been similarly investigated. High doses of diuretic are commonly used in hospitalised HF patients who have chronic severe left ventricular (LV) systolic dysfunction; however, data evaluating dose-response are lacking.

These concerns emphasize the need to further evaluate the relation between diuretic dose and clinical outcomes. We analyzed the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness (ESCAPE) trial database to describe the patterns of diuretic use, and to examine the relation between diuretic dose and clinical outcomes in patients with severe chronic HF admitted for an episode of decompensation (7).

## METHODS

We used the ESCAPE trial database for the analysis. The design of the ESCAPE trial has been previously published (7). Briefly, ESCAPE was a randomised trial of pulmonary artery catheter (PAC)-guided therapy versus standard therapy in patients hospitalised with decompensated HF. The study enrolled 433 patients. The primary endpoint was the number of days well, that is the number of days since randomisation the patient was neither dead nor hospitalised within 180 days after randomization. There was no statistically significant difference between groups for this primary endpoint. The primary data have been published (8).

We restricted the analyses to the 395 patients on diuretics (furosemide equivalent). Of these, 354 patients were on furosemide, and 41 patients were on torsemide. The torsemide doses were multiplied by 4 to convert to doses equivalent to furosemide. The conversion value of 4 is based on the results of Scheen et al (9). The maximum total daily dose of diuretics during hospitalisation was used as the dosing measure for this analysis.

As part of the ESCAPE trial, weight was captured at the time of randomization and at discharge. Weight determination was made by the same method (same scale), to the extent possible. Study coordinators recorded weights and key laboratory values such as sodium, blood urea nitrogen (BUN), and creatinine on the case report forms every other day. The total daily dose of loop diuretics was captured at randomization and discharge. In addition, the highest inhospital total daily dose of diuretics, duration of the highest dose, and route of administration were captured. Key baseline characteristics and the use of other HF medications, such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and inotropes were also recorded at randomization, during hospitalisation, and at discharge.

In-hospital weight change, defined as the difference in baseline weight (kg) and discharge weight in patients treated with diuretics during hospitalisation, was used as an estimate of fluid loss. If the patient's discharge weight was missing, then the 7-day weight, 5-day weight, or 3-day weight, in that order, were used in the calculation. Eighteen patients with missing weight data at all of these time-points were excluded from the weight analysis.

Multiple linear regression analysis was used to identify baseline predictors of observed weight loss. Baseline weight, age, BUN, serum creatinine, sex, length of initial hospitalisation (from randomization), brain natriuretic peptide (BNP), sodium, baseline diuretic use, ejection fraction, and diuretic dose were used as candidate variables.

Mortality was related to maximum in-hospital diuretic dose using a log-logistic model with a non-zero background. Because the response variable, mortality, is log-transformed, it was logical to also log-transform the independent variable (diuretic dose). This model was pre-specified based on previous analyses of the ESCAPE data. The non-zero background term specifically recognizes that even if the diuretic dose is zero, mortality is not zero. The model fitted was:

$$\Pr(death)=\gamma+\frac{1-\gamma}{1+e^{-\alpha-\beta Ln(dose)}}$$

where $\gamma$ is the background mortality rate, $\alpha$ is the intercept, and $\beta$ is the slope relating the maximum in-hospital diuretic dose to mortality. This model was used only for the univariate relation. A multiple logistic model, which adjusted for other known predictors of mortality based on the results of the ESCAPE trial (8) was also calculated. The model included terms for age, baseline BUN, and sodium. This adjustment was made to account for severity of illness, since it is possible that sicker patients would have received higher diuretic doses.

## RESULTS

The baseline characteristics of all patients who received diuretics are provided in Table 1. The median (25th, 75th) furosemide equivalent maximal daily dose in this population was 400 mg/day (160, 720). Seventeen percent of the patients lost no weight or actually gained weight. The median weight loss was 2.8 kg (interquartile range = 0.7 to 6.1).

We examined the relation of observed weight loss to diuretic dose (Figure 1). A significant relation was observed between weight loss and maximal diuretic dose ($t = 3.42$; $p = 0.0007$), but the $R^2$ value was very low ($R^2 = 0.030$). The results of the multiple linear regression analysis identified baseline weight, length of the initial hospitalisation (from randomization), and BNP as significant predictors of weight loss. The relation with weight was expected as heavier patients have the potential to lose more weight. Diuretic dose was not a significant predictor after adjusting for other factors (Table 2). The weight loss analyses were repeated including only furosemide patients and the results were nearly identical.

Figure 2 displays the fitted curve for the relation between diuretic dose and mortality. The estimated values of the parameters were $\gamma = 0.108$, $\alpha = -10.04$, and $\beta = 1.238$. In ESCAPE, the overall mortality was 19%. The model provides a good fit to the observed data (chi-square = 1.34 for 3 degrees of freedom; $p = 0.720$). The results suggest a strong dose-response relation with mortality (chi-square = 11.68; $p = 0.003$). The increase is particularly striking beginning at a dose of about 300 mg/day of furosemide. The multivariable model included terms for age, BUN, sodium, and diuretic dose. No other baseline variables were found to be predictive. The results are in Table 3. The same analysis was repeated for those patients on furosemide, resulting in a similar fit and similar significance levels.

The use of inotropes was forced into the mortality model. Inotrope use was a significant predictor of mortality (chi-square = 5.69; $p = 0.017$). Diuretic dose continued to predict mortality even after the addition of inotrope use to the model (chi-square = 9.21; $p = 0.0024$). There was a tendency to a relation between maximal diuretic dose and baseline

serum creatinine (r = 0.088; $p = 0.080$). Glomerular filtration rate was estimated using the simplified MDRD equation. The correlation between maximal diuretic dose and glomerular filtration rate was −0.1146 ($p = 0.023$). Because diuretics have the potential to worsen renal function, we evaluated the relation between maximal diuretic dose and change in creatinine level (discharge – baseline) and change in glomerular filtration rate. We observed a smaller correlation for the tendency to change in creatinine level (r = 0.043; $p = 0.412$) (Figure 3) and a smaller correlation for the change in glomerular filtration rate (r = −0.0149; $p = 0.777$).

## Discussion

This study reports 3 important findings concerning the consequences of diuretic dosing in patients hospitalised with severe decompensated HF due to LV systolic dysfunction. First, there was minimal association between maximum in-hospital diuretic dose and weight loss achieved, with higher doses failing to produce greater reductions in body weight. Based on the observed weight loss in the ESCAPE patients on diuretics, it is clear that the response range is wide. This could be because the dose was up-titrated to match urine output/weight loss. It is also possible that the equivalence of different daily doses in this study reflects different modes of administration. In addition, as kidney function decreases higher doses of diuretics are in demand to maintain similar diuretic effect. The same daily dose administered by constant diuretic infusion has been suggested to have more diuretic impact than intermittent boluses, and information was not collected to distinguish the two. The wide response range could be the result of clinicians quickly determining the optimal diuretic dose for each patient so that the weight loss would be independent of the dose. However, it does suggest that greatly increasing the dose in the absence of diuresis may not be particularly beneficial.

Secondly, we found that increasing diuretic dose was associated with increased risk of mortality at 6 months. This relation persisted after adjustment for multiple predictors of mortality previously identified in ESCAPE, including the use of inotropes. While our observational analysis cannot establish a cause and effect relation between high-dose diuretic and increased mortality, the results raise the concern that this relation is possible.

Finally, we observed that diuretic dose was associated with increases in serum creatinine from baseline to discharge. Although the association was modest, serum creatinine has been shown to be a predictor of mortality in several studies (1,2). In OPTIME, the presence of renal insufficiency more than doubled the risk of death or rehospitalisation at 60 days. In ADHERE, elevated BUN was the most important prognostic marker of in-hospital mortality. Given the previous work and our findings of an association between higher mortality and higher diuretic dose, the observation that higher diuretic doses were also associated with worsening renal function is a concern.

Although diuretics are effective in treating the signs and symptoms of congestion, data to guide dosing strategies are lacking. This lack of information presents a major challenge to the standard approach to managing acute decompensated HF.

A few studies have examined the potential toxicities associated with high-dose loop diuretics. Cotter et al. reported the results of a small study of 20 patients with refractory congestive HF (10). Patients were randomised to 1 of 3 groups: 1) low-dose dopamine and low-dose oral furosemide (40 mg orally twice daily); 2) low-dose dopamine and furosemide continuous infusion (5 mg/kg/day); and 3) high-dose furosemide continuous infusion (10 mg/kg/day). All patients experienced improvement in congestive symptoms, and weight loss was similar among groups. Both groups treated with intravenous furosemide experienced

significant decreases in mean arterial blood pressure and deterioration in renal function. The authors concluded that high-dose diuretics may be dangerous in this setting (10).

Another study by Cotter et al. evaluated the use of intravenous isosorbide dinitrate and intravenous furosemide in patients with acute HF and pulmonary oedema (11). This study compared high-dose nitrates (3 mg bolus every 5 minutes) + low-dose furosemide (40 mg bolus) with low-dose nitrates (1 mg/hour, doubled every 10 minutes) + high-dose furosemide (80 mg bolus every 15 minutes). Mechanical ventilation was required in more patients treated with high-dose furosemide (40% vs. 13%; $p = 0.0041$). The composite endpoint of death, mechanical ventilation, or myocardial infarction was also higher for the high-dose furosemide group (11).

Retrospective analyses from registries and clinical trials provide additional data suggesting that diuretics may be harmful (5,6). Data from the ADHERE registry suggest that patients treated with intravenous diuretics had higher in-hospital mortality, longer total length of stay, and longer length of stay in the intensive care unit as compared with patients who were not treated with intravenous diuretics, even after adjusting for other prognostic factors (5). Similar findings reported by Constanzo et al. demonstrated a higher in-hospital mortality and longer length of stay for patients enrolled in ADHERE who were treated with chronic diuretic therapy at the time of admission as compared with patients not treated with diuretics at the time of admission. The difference was even more pronounced in patients with serum creatinine ≥2mg/dL (6).

This analysis from ESCAPE was conducted in a decompensated population in whom intravenous diuretics were initiated. However, studies in the chronic HF population have also shown an independent association between diuretic use and increased mortality (12,13). An analysis from the Studies of Left Ventricular Dysfunction (SOLVD) trial demonstrated that all-cause and cardiovascular mortality rates were higher in patients receiving a diuretic at baseline (12). Additionally, on univariate and multivariate analysis, diuretic use was significantly associated with arrhythmic death. Similar findings were reported by the Prospective Randomised Amlodipine Survival Evaluation (PRAISE) investigators (13).

Several potential limitations should be considered when interpreting this analysis. First, we used weight change as a proxy measure of clinical benefit. This analysis does not consider the effect of diuretics on other endpoints such as dyspnoea. Second, higher diuretic use could have been a marker of a sicker patient at high risk of mortality regardless of diuretic therapy. Although we adjusted for known prognostic factors in our model, there are other factors unaccounted for which could have led to greater risk of death in patients treated with high-dose diuretics, and could account for the relation between diuretic dose and higher risk of death that we observed. Third, there are multiple ways in which diuretic dosing could have been assessed, including total dose while hospitalised and total maximum dose during hospitalisation (total days on maximal dose × maximal dose). These assessments could have been useful in evaluating the association between diuretic dose and outcomes. Furosemide doses change often in the acute setting. We only evaluated the association between outcome and maximal furosemide dose in this analysis. Patients could have received the maximal dose for varying lengths of time, which could not be accounted for in this analysis. Despite the limitations in our modeling analysis, these data are important for clinicians to consider as they care for patients with decompensated HF. Definitive results will require a prospective, randomised trial of diuretic dosing, which is not likely to be supported by the pharmaceutical industry. Financial support from government and/or academic organizations is needed to conduct such a trial.

## CONCLUSIONS

Our findings suggest that furosemide doses >300 mg/day may be associated with higher mortality, even after adjusting for measured risk factors. When aggressive dosing is prescribed, clinicians should use these doses with caution. More definitive answers should be obtained by performing a randomised controlled trial.

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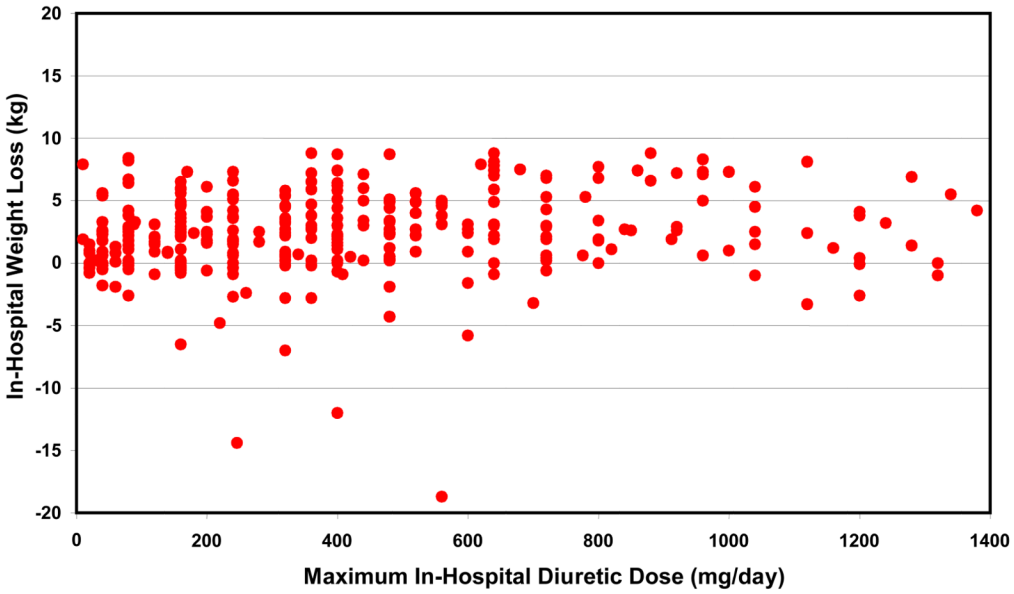


**Figure 1.**
Individual weight loss as a function of maximum in-hospital diuretic dose.

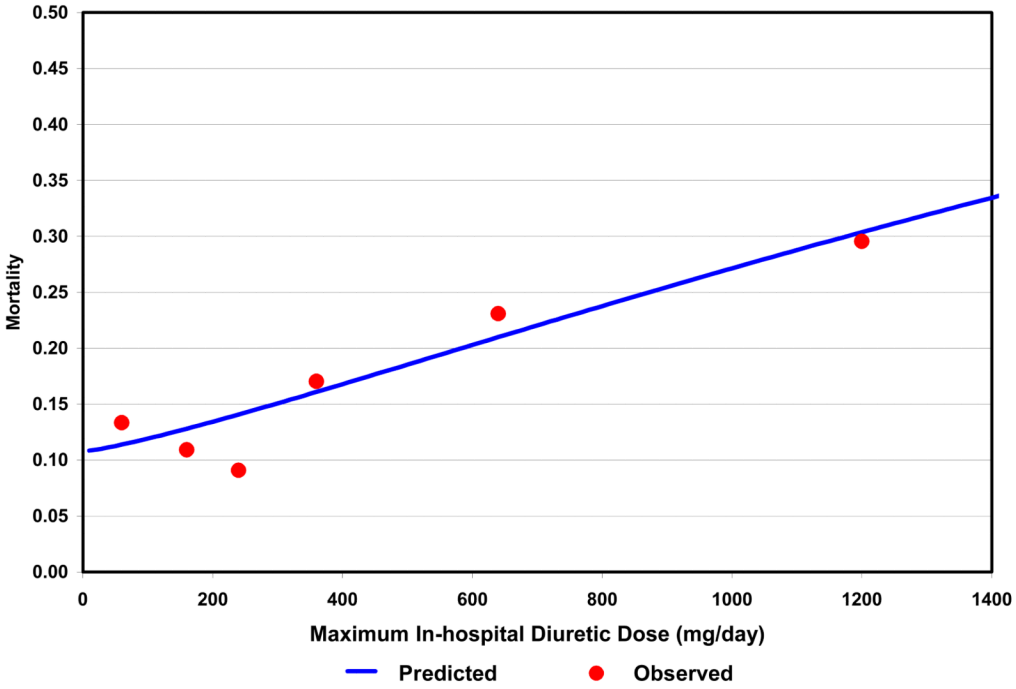


**Figure 2.**
Mortality as a function of maximum in-hospital diuretic dose.

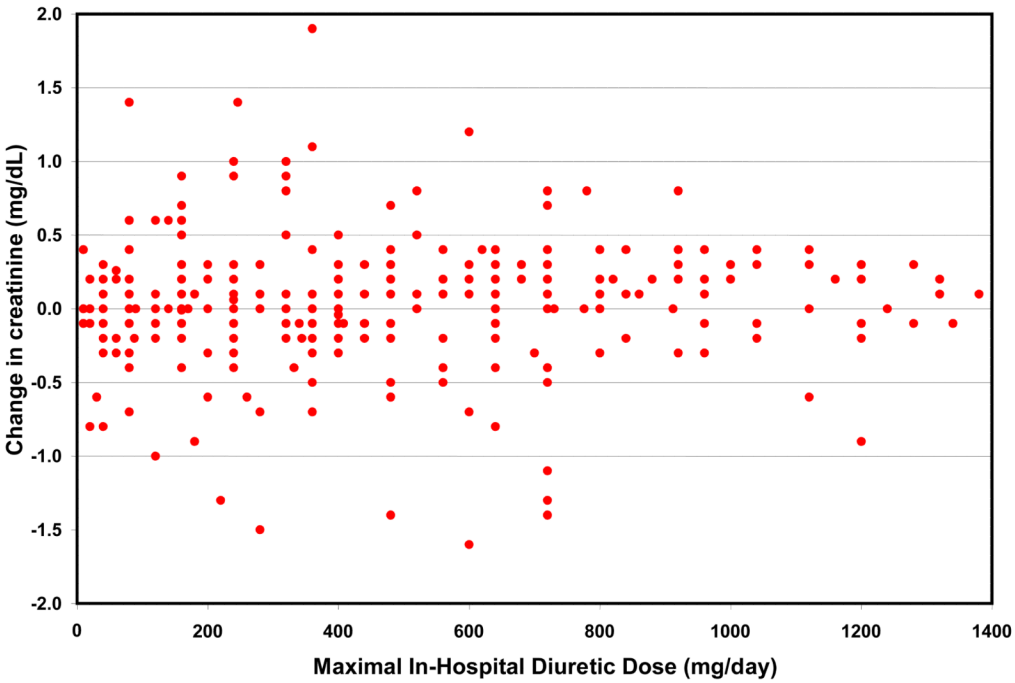


**Figure 3.**
Relation of maximal diuretic dose to discharge serum creatinine level.

## Table 1

Baseline Characteristics by Diuretic Dose

| | Dose ≤300 mg (n = 148) | Dose >300 mg (n = 247) | *p* value* |
|---|---|---|---|
| Age, mean ± SD, yrs | 58 ± 13 | 54 ± 14 | .010 |
| Sex, No. (%) | | | .037 |
| Male | 101 (68) | 192 (78) | |
| Female | 47 (32) | 55 (22) | |
| Race, No. (%) | | | .907 |
| White | 86 (58) | 145 (59) | |
| Minority | 62 (42) | 102 (41) | |
| Aetiology, No. (%) | | | .927 |
| Ischaemic | 75 (51) | 123 (50) | |
| Non-ischaemic | 73 (49) | 124 (50) | |
| EF, mean ± SD, % | 21 ± 7 | 19 ± 6 | .003 |
| Systolic BP, mean ± SD, mm Hg | 106 ± 17 | 106 ± 16 | .529 |
| Sodium, mean ± SD, mg/dL† | 137 ± 3.8 | 136 ± 4.7 | .072 |
| Potassium, mean ± SD, mg/dL | 4.3 ± 0.6 | 4.2 ± 0.7 | .014 |
| BUN, mean ± SD, mg/dL† | 31 ± 21 | 37 ± 23 | .007 |
| Creatinine, mean ± SD, mg/dL† | 1.5 ± 0.7 | 1.5 ± 0.6 | .360 |
| Baseline BNP, mean ± SD, pcg/mmol | 661 ± 845 | 1184 ± 1510 | < .001 |
| 6-minute walk, mean ± SD, ft | 421 ± 409 | 414 ± 420 | .913 |
| Baseline medications, No. (%) | | | |
| Potassium sparing diuretics | 75 (51) | 124 (50) | .927 |
| ACE inhibitors | 117 (79) | 195 (79) | .980 |
| Beta-blockers | 95 (65) | 148 (60) | .398 |
| Digoxin | 111 (75) | 176 (71) | .353 |

*Chi-square tests for rates, Wilcoxon rank sum tests for means.

†Normal ranges: creatinine 0.5–1.4; sodium 130–150; BUN 4–25. SD, standard deviation; EF, ejection fraction; BP, blood pressure; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; ACE, angiotensin-converting enzyme.

**Table 2**

Predictors of Weight Loss

| Parameter | Estimate | Std error | t value* | Pr > \|t\|† |
|---|---|---|---|---|
| Base weight, per 10 kg‡ | 0.757 | 0.141 | 5.37 | < 0.0001 |
| BNP, logarithm, pcg/mmol | 1.028 | 0.223 | 4.60 | < 0.0001 |
| Length initial hospitalisation, days | 0.084 | 0.050 | 1.69 | 0.0930 |
| Diuretic dose, logarithm, mg/day | 0.364 | 0.371 | 0.98 | 0.3275 |

BNP, brain natriuretic peptide.

*Student t value.

†Probability of getting an absolute t value this large due to chance (*p* value).

‡Regression coefficient calculated per 10 kg increase in weight.

**Table 3**

Multivariate Predictors of Mortality

| Term | HR | 95% CI | Chi-square | *p* value |
|---|---|---|---|---|
| Age >65 yrs | 1.100 | 1.043, 1.160 | 12.33 | .0004 |
| BUN (per 10), mg/dL | 1.215 | 1.086, 1.360 | 11.61 | .0007 |
| Sodium | 0.920 | 0.867, 0.977 | 7.39 | .0066 |
| Diuretic dose (per doubling) | 1.147 | 1.025, 1.282 | 5.76 | .0164 |

HR, hazard ratio; CI, confidence interval; BUN, blood urea nitrogen.